

The Enigmatic 13th Cranial Nerve: Anatomy, Function, and Clinical Significance of the Nervus Terminalis

Năstase Grigorie-Alexandru^{1,8}, Iftimie Nicolae-Florin⁸, Briceanu Oana-Georgiana⁸, Manole Maria⁸, Harter-Radu Miruna⁸, Cadar Ramona^{1,8}, Trofin Ana-Maria^{1,8}, Năstase Anda-Lucia³, Zabara Mihai^{1,8}, Buescu Ovidiu-David^{1,8}, Buzincu Iulian^{2,8}, Duvac Rares-Cristian⁴, Tailup Roxana⁶, Akad Fawzy⁷, Lupașcu Ursulescu Corina^{6,8}, Vasilescu Alin-Mihai^{5,8}, Vlad Nuțu^{5,8}, Lupașcu Cristian Dumitru^{1,8}

1. Saint Spiridon Emergency County Hospital Iași, 2nd Surgery and Liver Transplant Clinic

2. Saint Spiridon Emergency County Hospital Iași, Anesthesia and Intensive Care Unit

3. Regional Institute of Oncology Iași. Anesthesia and Intensive Care Unit

4. Saint Spiridon Emergency County Hospital Iași, Clinical Pharmacology Department

5. Saint Spiridon Emergency County Hospital Iași, 1st Surgery Clinic

6. Saint Spiridon Emergency County Hospital Iași, Radiology department

7. University of Medicine and Pharmacy "Grigore T. Popa" Iași, Morpho-Functional Sciences I, Anatomy

8. University of Medicine and Pharmacy "Grigore T. Popa" Iași, Faculty of Medicine, Romania

Abstract. Introduction. The Nervus Terminalis (NT), also known as cranial nerve XIII or cranial nerve 0, is an underrecognized component of the nervous system. Traditionally overlooked, recent studies highlight its unique structure and potential physiological role. It has been identified in human cadaveric specimens, suggesting its consistent presence within the cranial nerve system. **Aim.** This review aims to analyze the Nervus Terminalis, including its historical background, structural features, physiological functions, and possible role in neurological disorders, to enhance understanding and highlight areas for further research. **Method:** A comprehensive literature review was conducted using databases such as PubMed and Clarivate. **Keywords** included Nervus Terminalis, Cranial Nerve XIII, Cranial Nerve 0, Gonadotropin-Releasing Hormone, and Evolutionary Neuroscience of Cranial Nerves. The review included peer-reviewed studies on NT's anatomy, neurochemistry, and clinical relevance, as well as immunohistochemical, neuroimaging, and molecular biology research. **Results.** NT is a small, bilaterally paired nerve closely linked to the olfactory system. It extends into key brain regions, including the hypothalamus, and contains gonadotropin-releasing hormone (GnRH)-producing neurons, reinforcing its role in endocrine regulation. Studies indicate that 89.9% of GnRH-positive NT neurons express ACE2, while 9.4% of cholinergic NT neurons express ACE2, suggesting its possible involvement in viral neuroinvasion. Additionally, NT contributes to sensory modulation, autonomic processes, and early neurodevelopment, forming critical connections with the hypothalamus during embryogenesis. Neuroimaging studies confirm its presence in adult human brains, supporting its relevance in neurophysiology. **Conclusions.** The Nervus Terminalis plays an essential role in sensory and endocrine integration but remains underrecognized. Further research is needed to clarify its involvement in disease mechanisms and neurodevelopment. Future studies should focus on functional imaging, molecular characterization, and its potential impact on neurodevelopmental and neurodegenerative disorders.

Key words: nervus terminalis, cranial nerve XIII, cranial nerve 0, gonadotropin-releasing hormone

Corresponding author: Iftimie Nicolae-Florin, iftimienicolaeflorin@yahoo.com

Received: January 30, 2025; **Accepted March** 10, 2025; **Published March** 31, 2025

Citation: Năstase G.-Al., Iftimie N. Fl., Briceanu Oana-Georgiana, Manole Maria, Harter-Radu Miruna, Cadar Ramona¹, Trofin Ana-Maria, Năstase Anda-Lucia, Zabara M., Buescu O.D., Buzincu I. Duvac R.Cr., Tailup Roxana, Fawzy A., Lupașcu Ursulescu Corina, Vasilescu Al.M.

Vlad N., Lupașcu Cr. D. The Enigmatic 13th Cranial Nerve: Anatomy, Function, and Clinical Significance of the Nervus Terminalis. [Journal of Surgery [Jurnalul de chirurgie]. 2025; 21(1): 8 - 17, DOI: 10.22551/JSURG.2025.01.02

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I. Introduction

The Nervus Terminalis (NT), often referred to as cranial nerve XIII or cranial nerve 0, has historically been an overlooked aspect of neuroanatomy. Initially identified in the early 20th century, its existence in humans was debated for years. However, recent anatomical and neuroimaging studies have confirmed its presence across various vertebrate species, including humans (1). NT stands apart from other cranial nerves due to its distinct neurochemical properties, its connections to the hypothalamus, and its possible involvement in endocrine regulation (2). NT was first identified by Johnston (1905) in sharks and amphibians, where it was observed projecting toward the forebrain and hypothalamus (1). Later research demonstrated its presence in mammals, including primates and humans, where it was identified in both fetal and adult specimens (2). Despite these findings, NT was frequently omitted from traditional cranial nerve classifications due to its small size and unclear function (3).

In human embryonic development, NT is among the first cranial nerves to emerge, forming from neural crest cells near the olfactory placode (4). Its projections extend to the hypothalamus, septal nuclei, and limbic system, suggesting its involvement in reproductive behaviors, autonomic regulation, and sensory processing (2).

Recent advances in neuroimaging and molecular biology have sparked renewed interest in NT. Studies utilizing immunohistochemical techniques have demonstrated that NT contains gonadotropin-releasing hormone (GnRH)-producing neurons, further supporting its role in neuroendocrine signaling (5). Furthermore, 89.9% of GnRH-positive NT neurons express ACE2, which has implications for viral neuroinvasion and neuropathological conditions (5).

Anatomy of the Nervus Terminalis

Location and Anatomical Course

The Nervus Terminalis (NT) is a delicate, bilaterally paired nerve positioned adjacent to the olfactory nerve (CN I), extending toward the forebrain, hypothalamus, and limbic structures. It originates in the nasal cavity, coursing along the olfactory tract (fig.1), yet remaining functionally distinct due to its complex fiber network and neuromodulatory role (6). Unlike conventional cranial nerves, NT does not form a single unified pathway but instead comprises a diffuse plexus of unmyelinated fibers, interweaving through different autonomic and sensory structures (6).

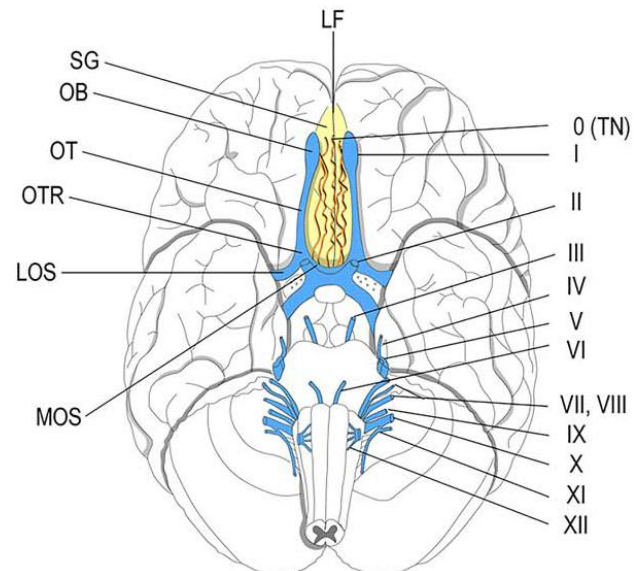


Fig.1 Schematic representation of the NT intracranial course in the adult human brain. LF=longitudinal fissure, SG=straight gyrus, OB=olfactory bulb, OT= olfactory tract, OTR=olfactory trigone, LOS=lateral olfactory stria, MOS=medial olfactory stria, TN = nervus terminalis. (from Peña-Melián, 2018)

NT has been extensively mapped using neurotracing techniques, revealing its extensive projections into the septal nuclei, amygdala, and hypothalamus. These anatomical connections suggest its involvement in autonomic regulation, reproductive behavior, and sensory processing (1). The NT's structural design indicates that rather than functioning as a primary sensory nerve, it modulates signals that influence hormonal regulation, memory encoding, and behavioral adaptation (2). Some researchers propose that the NT's organization resembles

autonomic ganglia, further supporting its role in homeostatic and neuroendocrine integration (6).

Embryological Development

The development of NT is evident from the earliest stages of embryogenesis, emerging from neural crest cells located near the olfactory placode (7)(8). As the embryonic brain forms, NT migrates toward the hypothalamus and limbic system, playing an essential role in early neural circuit formation, hormonal signaling, and autonomic control (2)(9).

One of NT's key embryological functions is its role in GnRH neuron migration(10)(11). During development, gonadotropin-releasing hormone (GnRH)-producing neurons travel along NT fibers, establishing connections with the hypothalamic-pituitary-gonadal axis (12)(13). This migration is fundamental for proper reproductive endocrinology, and defects in NT development have been linked to Kallmann Syndrome (14), a disorder that results in olfactory dysfunction and hypogonadotropic hypogonadism (6).

Comparative embryological studies indicate that NT follows a highly conserved developmental pattern across various species, including fish, amphibians, reptiles, and mammals, highlighting its evolutionary significance (6). The nerve is particularly pronounced in early developmental stages (fig.2), emphasizing its critical role in guiding olfactory and neuroendocrine networks (2). In mammalian species, NT forms stable connections with the hypothalamus and limbic structures, reinforcing its function in hormonal regulation and behavioral modulation as the organism matures (15).

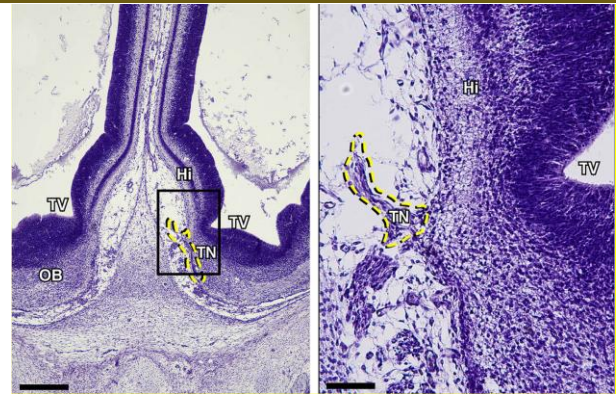


Fig.2 Coronal section of human embryo brain (hematoxylin-eosin staining) depicting NT's fibers entering the telencephalon and nearby hippocampus. Scale: 500µm (left picture), 100 µm(right picture). TN=nervus terminalis, TV=telencephalic vesicle, OB=olfactory bulb, Hi=hippocampus. (from Peña-Melián, 2018)

Relationship with Other Cranial Nerves

NT shares anatomical and functional relationships with several cranial nerves, reinforcing its integrative role in sensory and autonomic functions. While closely associated with CN I (Olfactory Nerve) (16), NT does not contribute directly to odor perception but rather modulates pheromone-related cues and neuroendocrine responses (2).

Additionally, NT has documented interactions with the trigeminal nerve (CN V) (17) and autonomic pathways, suggesting its involvement in visceral sensory processing and autonomic homeostasis (6). These connections imply that NT may influence subconscious responses to pheromones, affecting social behaviors, reproductive signaling, and hormonal regulation (5).

NT also interacts with the hypoglossal nerve (CN XII) and cranial nerves responsible for motor coordination and autonomic integration, suggesting its participation in involuntary physiological responses to environmental stimuli (1). Some researchers hypothesize that NT may mediate pheromone-induced autonomic reactions, such as changes in heart rate, blood pressure, and hormonal fluctuations (6). The presence of NT fibers near brainstem autonomic nuclei further supports this hypothesis, indicating its involvement in regulating involuntary physiological adjustments (2).

III. Function and Physiological Role Sensory and Autonomic Functions

NT has been implicated in both sensory processing and autonomic regulation, playing a distinct role in neural integration (18). Unlike other cranial nerves that serve direct sensory or motor functions, NT acts as a modulatory structure, influencing autonomic stability, cardiovascular regulation, and hormonal signaling (19).

Anatomical evidence suggests that NT projects to key regions within the autonomic nervous system, including the preoptic area of the hypothalamus and the septal nuclei, which are involved in thermoregulation, cardiovascular responses, and metabolic control (20). Additionally, NT interacts with brainstem autonomic centers, suggesting its involvement in modulating unconscious physiological responses, such as heart rate and respiratory regulation (2).

Association with Pheromone Signaling and Reproductive Behavior

Studies have demonstrated that lesions or developmental defects affecting NT can lead to altered reproductive behaviors, disruptions in gonadotropin release, and reduced mating success, reinforcing its critical role in reproductive endocrinology (21). Furthermore, NT plays an essential part in the migration of GnRH-producing neurons (22), which are responsible for coordinating reproductive hormone release via the hypothalamic-pituitary-gonadal axis (23).

Connection with the Limbic System

NT's projections extend into the amygdala, hippocampus, and hypothalamus, positioning it as an important player in emotional processing, memory formation, and instinctual behaviors (24).

Through its extensive connectivity, NT may regulate emotionally driven behaviors such as social bonding, stress responses, and fear modulation (19).

Furthermore, its connections to the septal nuclei and prefrontal cortex suggest NT's role in higher-order cognitive processing,

including decision-making and motivational behaviors. Some researchers propose that NT serves as an intermediary between sensory perception, emotional states, and autonomic reflexes, modulating adaptive physiological responses to environmental changes (25).

IV. Clinical and Neurophysiological Significance

Role in Human Cognition and Behavior

Emerging research highlights NT's potential impact on cognitive functions and behavioral responses, particularly its influence on decision-making, reward processing, sensory-motor integration, and memory consolidation. NT's pathways to the prefrontal cortex, hippocampus, and limbic structures indicate a possible role in higher-order cognition, affecting problem-solving, emotional intelligence, learning, and social behavior (25).

Some studies suggest that NT influences subconscious behavioral patterns, contributing to habit formation, conditioned responses, and autonomic emotional regulation. Given its extensive neuroanatomical distribution, NT could act as a mediator between innate sensory-driven behaviors and conscious cognitive processes, allowing for adaptations in response to environmental challenges and long-term behavioral plasticity (23).

Additionally, NT's involvement in neurodevelopmental processes suggests that it may contribute to adaptive behaviors during early life, impacting social interactions, bonding, and stress-coping mechanisms. The presence of NT in regions associated with dopaminergic signaling and reward processing also implies that it may have a function in motivation, pleasure-seeking behaviors, and addiction susceptibility (19).

Potential Involvement in Neuropsychiatric Disorders

There is increasing speculation that NT may play a role in neuropsychiatric conditions,

particularly those involving sensory processing deficits, mood dysregulation, autonomic dysfunction, and social impairments(26) Some researchers have proposed that NT dysfunction may be implicated in anxiety disorders, schizophrenia, depression, and social communication deficits, particularly those observed in autism spectrum disorders and bipolar disorder (24).

Alterations in NT's connections with the limbic system could contribute to abnormal fear responses, heightened stress reactivity, emotional instability, and maladaptive coping strategies. Additionally, given NT's role in modulating the hypothalamic-pituitary-adrenal axis, disruptions in its function may influence cortisol secretion patterns, leading to impaired stress adaptation, mood instability, and vulnerability to chronic stress-related disorders (19).

Recent genetic and functional studies suggest that mutations affecting NT pathways may contribute to developmental disorders such as ADHD, OCD, and PTSD, supporting the idea that NT participates in attention regulation, impulse control, and emotional resilience. Dysfunctions in NT-related circuits could also be involved in eating disorders, obsessive tendencies, and maladaptive compulsions, particularly those linked to dopaminergic and serotonergic imbalances (23).

Potential Role in Viral Infections

Recent studies have suggested that NT may serve as a pathway for viral invasion into the central nervous system (CNS). Given its proximity to the olfactory system and connections with the hypothalamus, NT has been identified as a possible route for neurotropic viruses, including SARS-CoV-2, herpesviruses, and influenza viruses (19).

Research has demonstrated that ACE2

receptors, which facilitate viral entry into cells, are expressed in 89.9% of GnRH-positive NT neurons, suggesting that NT may play a role in olfactory-related neuroinvasion (23). This could explain some of the neurological symptoms associated with viral infections, such as anosmia, cognitive dysfunction, autonomic instability, and neuroinflammatory responses (24).

Furthermore, viral infiltration via NT may contribute to long-term neurodegenerative consequences, potentially exacerbating Alzheimer's disease, Parkinson's disease, and multiple sclerosis. Inflammatory markers associated with NT dysfunction post-viral infection have been found in patients suffering from long-term cognitive deficits, chronic fatigue syndrome, and post-viral autonomic disorders, further reinforcing its role in neurological sequelae following infection (19).

Understanding NT's role in viral transmission pathways and post-infection neurological complications may open new avenues for therapeutic interventions, including targeted antiviral treatments, neuroprotective therapies, and immunomodulatory strategies for preventing long-term CNS damage (19).

Experimental and Anatomical Studies Supporting Its Function

Recent studies using functional MRI, electrophysiological recordings, neural tracing, and immunohistochemical mapping have provided direct evidence of NT's activity in response to sensory, hormonal, and social stimuli. Neural tracing techniques have confirmed NT's extensive connectivity with autonomic and neuroendocrine centers, reinforcing its role as a neuromodulatory integrator and behavioral regulator (2).

Lesion studies have further demonstrated NT's role in pheromone detection, stress regulation, and reproductive behavior, highlighting the importance of this cranial nerve in subconscious physiological adaptations.

Stimulation of NT fibers has been shown to influence heart rate variability, emotional arousal, and endocrine feedback loops, further supporting its role in neurophysiological homeostasis (24).

Future research utilizing optogenetic stimulation, deep-brain imaging, and viral vector tracing may help elucidate NT's precise role in cognitive, emotional, and physiological regulation, paving the way for potential clinical applications in neurological, neuropsychiatric, and infectious disease research.

The integration of NT into broader neurological frameworks may offer new insights into its function in human behavior, neuroimmune interactions, and CNS disorders, allowing for more targeted therapeutic interventions for neurological and psychiatric conditions.

V. Comparative Anatomy and Evolutionary Perspective

Presence in Other Species (Vertebrates and Mammals)

The Nervus Terminalis (NT) is highly conserved across vertebrate species, suggesting that it serves a fundamental biological function beyond humans (27). First identified in cartilaginous fish – sharks (fig3), NT has been found in amphibians, reptiles, birds, and mammals, indicating its evolutionary significance (20). In non-mammalian species, NT is often more prominent, particularly in those that rely heavily on chemosensory communication for survival and reproduction (28).

In fish and amphibians, NT plays a crucial role in pheromone detection and reproductive behaviors, allowing these species to respond to environmental chemical cues essential for

mating and territory marking (19). Studies in teleost fish have revealed strong NT projections to the preoptic area of the hypothalamus, reinforcing its role in hormonal and autonomic regulation (12). Similarly, in amphibians, NT has been linked to water balance, seasonal breeding cycles, and olfactory-driven navigation.

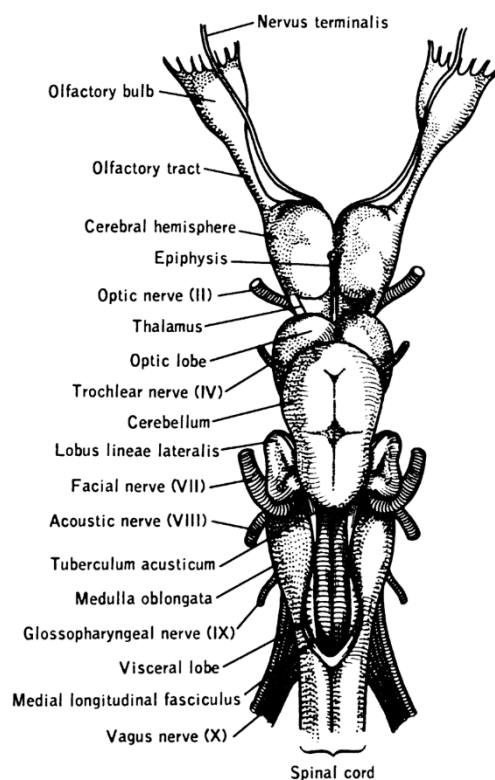


Fig.3 Illustration of the posterior view of a dogfish shark, nervus terminalis being present medially to the olfactory tracts. (from the book "A functional approach to neuroanatomy" – 1960, adapted from Ronton and Clark – The Anatomy of the Nervous System, 10th ed., W.B. Sanders Company, Philadelphia, 1959)

In reptiles and birds, NT appears to function as an intermediary between the olfactory system and neuroendocrine centers, particularly in species where vomeronasal communication is a dominant factor in social and predatory behaviors. The structural differences observed in NT across these species suggest an adaptation of its function to meet the needs of different environmental demands.

In mammals, NT persists but exhibits significant variability in size and complexity, with some species demonstrating more extensive

NT projections to limbic and hypothalamic structures. Studies in rodents and primates show that NT plays a role in pheromone-guided behaviors, social interaction, and reproductive regulation, particularly through its interactions with the vomeronasal organ and hypothalamus (30). This suggests that NT may have evolved to integrate olfactory and endocrine signals in complex social environments.

Evolutionary Hypotheses About Its Persistence in Humans

Despite being less structurally prominent in humans, NT has not been lost during evolution, which raises questions about its continued relevance in higher primates. Several hypotheses have been proposed to explain its persistence:

1. **Neuromodulatory Integration Hypothesis:** NT may have evolved from being a direct sensory processing system in lower vertebrates to acting as a neuromodulator influencing cognition, emotional states, and autonomic functions in higher mammals (31). This aligns with NT's anatomical connections to the limbic system, hypothalamus, and autonomic regulatory centers.
2. **Olfactory and Social Processing Hypothesis:** While the reliance on pheromone-driven behavior has diminished in humans, NT may still contribute to subconscious sensory processing related to interpersonal interactions, emotional recognition, and stress responses (24). This would explain NT's projections into emotionally relevant brain regions such as the amygdala and hippocampus.
3. **Neuroimmune and Stress Response Hypothesis:** Some researchers suggest that NT plays a protective role in immune responses, particularly in stress adaptation and neuroinflammation control (19). Given NT's link to the hypothalamic-pituitary-adrenal axis, it may influence adaptive mechanisms in response to environmental stressors.
4. **Vestigial Structure Hypothesis:** Another

theory posits that NT represents a vestigial remnant of a once-functional sensory system that was more active in early human ancestors but has lost its primary function due to changes in social communication and sensory reliance (19). However, the fact that NT remains functional in autonomic and neuroendocrine pathways argues against it being entirely vestigial.

VI. Conclusion

The Nervus Terminalis is a largely overlooked yet functionally significant neural structure. While historically debated, modern research has confirmed its presence across vertebrate species and its integration within autonomic and neuroendocrine systems. NT's primary roles include modulating autonomic functions, contributing to pheromone-mediated behavior, and influencing neuroendocrine pathways, particularly through its connections with the hypothalamus, limbic system, and olfactory circuits.

Although its role in humans remains incompletely understood, emerging neuroimaging and electrophysiological evidence indicates that NT may be involved in stress adaptation, emotional regulation, and social behavior. Additionally, its potential role in viral neuroinvasion and immune interactions has led to growing interest in its implications for post-viral syndromes and neuroimmune disorders. NT's evolutionary persistence further suggests that it retains regulatory and sensory integration functions, even if its prominence has diminished in humans compared to other species.

Despite increasing recognition of NT's significance, further research is necessary to fully define its physiological and medical relevance.

NOTES

*All authors contributed equally to this work.

#Corresponding author.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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